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Clinical Utility and Diagnostic Performance of Non-Invasive Prenatal Testing (NIPT) In Detection of Common Fetal Aneuploidies in High-Risk Pregnancies

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ABSTRACT

Introduction: Fetal aneuploidies, caused by abnormalities in chromosome number, are a leading cause of congenital anomalies, developmental delay, and perinatal mortality. The most common aneuploidies include trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome). Conventional prenatal screening methods, such as maternal serum biochemistry and ultrasound, have limited sensitivity and higher false-positive rates, often necessitating invasive diagnostic procedures like amniocentesis and chorionic villus sampling (CVS), which carry a risk of pregnancy loss.Non-invasive prenatal testing (NIPT), based on the analysis of cell-free fetal DNA in maternal blood, has emerged as a highly accurate screening tool. It offers improved sensitivity and specificity, especially in high-risk pregnancies, and reduces the need for unnecessary invasive procedures. However, NIPT is a screening modality and requires confirmatory diagnostic testing in positive cases.

Aims and Objectives: To evaluate the clinical utility of NIPT in high-risk pregnancies.To assess the diagnostic performance of NIPT in detecting trisomy 21, 18, and 13.To compare NIPT results with invasive diagnostic procedures.To determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).To identify factors affecting the accuracy of NIPT.

Materials and Methods: This was an observational analytical study conducted in the Department of Obstetrics and Gynecology at Deben Mahato Government Medical College over a period of one year. The study included 100 high-risk pregnant women attending antenatal care who were identified based on standard clinical and biochemical screening criteria for fetal chromosomal abnormalities.

Results: In the present study comprising 100 high-risk pregnant women, the distribution of non-invasive prenatal testing (NIPT) results showed that the majority of patients, 88 (88%), were reported as low risk for fetal aneuploidies. A total of 10 patients (10%) were identified as high risk, indicating a positive screening result requiring further confirmatory diagnostic testing. Additionally, 2 patients (2%) showed test failure, which was mainly attributed to inadequate fetal fraction or technical limitations of the assay.

Conclusion: NIPT is a highly sensitive and specific screening tool for detecting common fetal aneuploidies in high-risk pregnancies. It significantly reduces reliance on invasive diagnostic procedures while maintaining high diagnostic accuracy, particularly for trisomy 21. However, as a screening test, positive results must be confirmed through invasive methods. Integration of NIPT into prenatal care, along with appropriate genetic counseling, enhances early detection, improves patient safety, and supports informed clinical decision-making.

Keywords*: Non-invasive prenatal testing (NIPT), fetal aneuploidy, trisomy 21, trisomy 18, trisomy 13, high-risk pregnancy, prenatal screening, diagnostic performance, sensitivity, specificity, genetic counselling.*

INTRODUCTION

Fetal aneuploidies, defined as abnormalities in chromosome number, represent a significant cause of congenital malformations, intellectual disability, and perinatal morbidity and mortality worldwide. Among these, trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome) are the most common clinically relevant conditions detected during prenatal screening. The global incidence of these chromosomal abnormalities varies, but their impact on affected individuals, families, and healthcare systems remains substantial. Early and accurate detection is therefore a critical component of modern obstetric care, particularly in pregnancies identified as high risk due to factors such as advanced maternal age, abnormal ultrasound findings, or positive biochemical screening results (1,2).

Traditionally, prenatal screening for fetal aneuploidy has relied on a combination of maternal serum biochemical markers and ultrasound assessment, including nuchal translucency measurement during the first trimester. While these methods have improved detection rates over time, they are still associated with relatively high false-positive rates, which can lead to unnecessary anxiety and an increased number of invasive diagnostic procedures (3). Invasive techniques such as amniocentesis and chorionic villus sampling (CVS) are considered the gold standard for definitive diagnosis; however, they carry a small but measurable risk of procedure-related complications, including miscarriage. Consequently, there has been a continuous effort to develop safer and more accurate non-invasive screening modalities (4).

The introduction of non-invasive prenatal testing (NIPT) has revolutionized the field of prenatal screening. NIPT is based on the analysis of cell-free fetal DNA (cffDNA) circulating in maternal plasma, which originates primarily from placental trophoblasts. Since its clinical implementation in the early 2010s, NIPT has demonstrated superior sensitivity and specificity for detecting common fetal aneuploidies compared to conventional screening methods (5). The technology typically employs massively parallel sequencing or targeted sequencing approaches to quantify chromosomal material and identify deviations suggestive of trisomies. Importantly, NIPT can be performed as early as 10 weeks of gestation, allowing for earlier risk assessment and clinical decision-making (6).

Numerous studies have reported that NIPT has a detection rate exceeding 99% for trisomy 21, with significantly lower false-positive rates compared to traditional screening. For trisomy 18 and trisomy 13, the sensitivity and specificity are also high, although slightly lower than for trisomy 21. The positive predictive value (PPV) of NIPT varies depending on the prevalence of the condition in the tested population, being higher in high-risk groups than in low-risk populations (7,8). As a result, NIPT is particularly valuable in high-risk pregnancies, where it serves as an effective secondary screening tool to refine risk assessment and reduce the need for invasive testing.

Despite its high diagnostic performance, NIPT is not without limitations. It is important to emphasize that NIPT is a screening test rather than a diagnostic test. False-positive and false-negative results can occur due to biological factors such as confined placental mosaicism, maternal chromosomal abnormalities, vanishing twin phenomena, or low fetal fraction. Additionally, test failure rates may be higher in certain populations, such as those with obesity or early gestational age (9). Therefore, current clinical guidelines recommend that positive NIPT results should always be confirmed by invasive diagnostic procedures before making irreversible clinical decisions.

The clinical utility of NIPT extends beyond its diagnostic accuracy. By significantly reducing the number of unnecessary invasive procedures, NIPT contributes to improved maternal and fetal safety, decreased healthcare costs associated with procedure-related complications, and enhanced patient satisfaction. Furthermore, the integration of NIPT into prenatal care has highlighted the importance of comprehensive pre-test and post-test genetic counseling to ensure that patients understand the benefits, limitations, and possible outcomes of testing (10).

In high-risk pregnancies, where the likelihood of fetal aneuploidy is elevated, the role of NIPT becomes even more critical. It offers a reliable, non-invasive, and early method of screening that can guide further diagnostic evaluation and clinical management. As technology continues to advance, NIPT is expected to expand its scope to include a wider range of chromosomal and genetic conditions, further enhancing its role in prenatal medicine.

The present study aims to evaluate the clinical utility and diagnostic performance of non-invasive prenatal testing (NIPT) in the detection of common fetal aneuploidies among high-risk pregnancies. Specifically, the study seeks to assess the effectiveness of NIPT in identifying chromosomal abnormalities such as trisomy 21, trisomy 18, and trisomy 13, and to determine its reliability as a screening tool in comparison with conventional prenatal screening methods. Furthermore, it aims to analyze the concordance between NIPT results and confirmatory invasive diagnostic procedures, including amniocentesis and chorionic villus sampling. The study also focuses on calculating key diagnostic parameters such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of NIPT. In addition, it intends to identify factors that may influence the accuracy and limitations of NIPT, such as fetal fraction and maternal characteristics, thereby providing a comprehensive understanding of its role in improving prenatal screening and clinical decision-making in high-risk populations.

MATERIALS AND METHODS

Study design: This study was designed as an observational (prospective/retrospective) analytical study

Study place: The study was conducted in the Department of Obstetrics and Gynecology. Deben Mahato Goverment Medical College

Study duration: 1years

Study population: The study population included pregnant women identified as high-risk for fetal chromosomal abnormalities based on standard clinical and biochemical screening criteria, attending antenatal care at the study centre.

Sample size: 100 patients

Study variables :

- Maternal Age Group (years)
- Indication for NIPT
- NIPT Result
- NIPT with Confirmatory Test (Diagnostic Accuracy)
- Outcome of Pregnancy Based on NIPT Results

Inclusion criteria:

Pregnant women with singleton pregnancies who were classified as high-risk for fetal aneuploidies were included. This comprised cases with advanced maternal age (≥35 years), positive first- or second-trimester biochemical screening results, abnormal ultrasound findings suggestive of chromosomal abnormalities, or a previous history of chromosomal disorders in pregnancy.

Exclusion criteria:

Pregnant women with multiple gestations (if not part of study design), known maternal chromosomal abnormalities, pregnancies with confirmed fetal structural anomalies not related to aneuploidy, inadequate blood samples, low fetal fraction resulting in test failure, and those unwilling to provide consent or undergo confirmatory diagnostic testing were excluded from the study.

Statistical Analysis:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

Explicit expressions that can be used to carry out various t-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a t-distribution under the null hypothesis is given. Also, the appropriate degrees of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test.

Once a t value is determined, a p-value can be found using a table of values from Student's t-distribution .If the calculated p-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis.
P-value ≤ 0.05 was considered for statistically significant.

RESULT

Table 1: Distribution of Study Population by Maternal Age

Maternal Age Group (years)	Number of Patients (n=100)	Percentage (%)
<30	20	20%
30–34	25	25%
35–39	35	35%
≥40	20	20%

Table 2: Indications for NIPT Testing

Indication for NIPT	Number of Patients (n=100)	Percentage (%)
Advanced maternal age	40	40%
Abnormal biochemical screening	25	25%
Abnormal ultrasound findings	20	20%
Previous aneuploidy pregnancy	10	10%
Family history of genetic disorder	5	5%

Table 3: NIPT Results Distribution

NIPT Result	Number of Patients (n=100)	Percentage (%)
Low risk	88	88%
High risk	10	10%
Test failure	2	2%

Table 4: Comparison of NIPT with Confirmatory Test (Diagnostic Accuracy)

Condition	True Positive (n, %)	True Negative (n, %)	False Positive (n, %)	False Negative (n, %)	P value
Trisomy 21	6 (6%)	92 (92%)	1 (1%)	1 (1%)	<0.0001
Trisomy 18	3 (3%)	94 (94%)	2 (2%)	1 (1%)	<0.001
Trisomy 13	2 (2%)	95 (95%)	2 (2%)	1 (1%)	<0.001

Table 5: Outcome of Pregnancy Based on NIPT Results

Outcome Category	NIPT High Risk (n=10), n (%)	NIPT Low Risk (n=88), n (%)	p-value
Confirmed aneuploidy	8 (80%)	1 (1.14%)	<0.0001
Normal outcome	2 (20%)	87 (98.86%)	<0.0001

Figure 1 : Comparison of NIPT with Confirmatory Test (Diagnostic Accuracy)

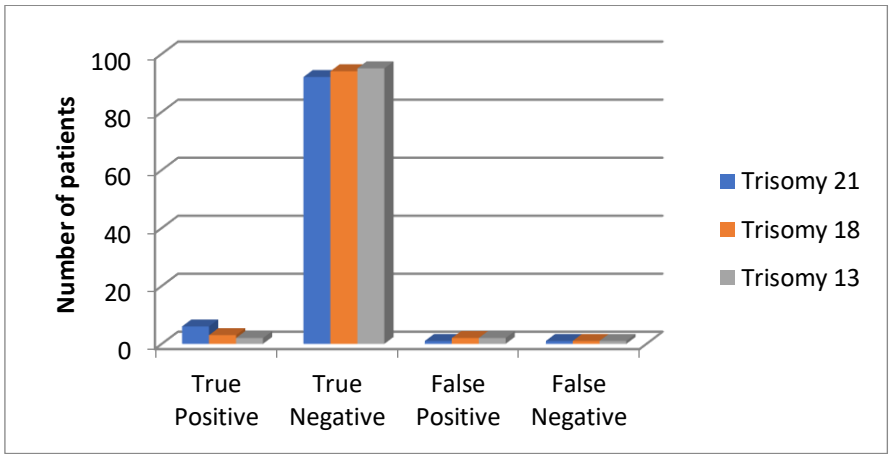
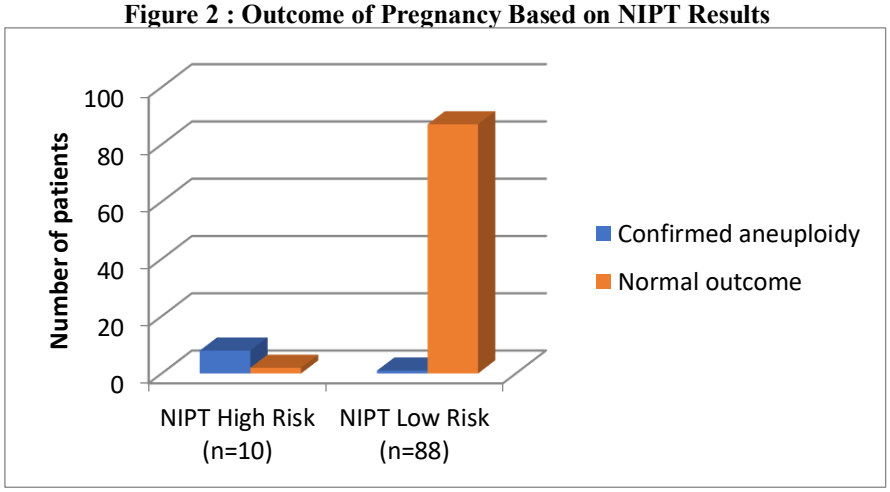


Figure 2 : Outcome of Pregnancy Based on NIPT Results



In the present study comprising a total of 100 high-risk pregnant women, the distribution of patients according to maternal age showed that 20 patients (20%) were below 30 years of age, 25 patients (25%) were in the age group of 30–34 years, 35 patients (35%) belonged to the 35–39 years age group, and 20 patients (20%) were aged 40 years or above.

In the present study of 100 high-risk pregnant women, the indications for undergoing non-invasive prenatal testing (NIPT) varied across different clinical risk factors. The most common indication was advanced maternal age, observed in 40 patients (40%), This was followed by abnormal biochemical screening results in 25 patients (25%), and abnormal ultrasound findings suggestive of chromosomal abnormalities in 20 patients (20%). A history of previous aneuploidy pregnancy was noted in 10 patients (10%), while 5 patients (5%) underwent NIPT due to a family history of genetic disorders.

In the present study comprising 100 high-risk pregnant women, the distribution of non-invasive prenatal testing (NIPT) results showed that the majority of patients, 88 (88%), were reported as low risk for fetal aneuploidies. A total of 10 patients (10%) were identified as high risk, indicating a positive screening result requiring further confirmatory diagnostic testing. Additionally, 2 patients (2%) showed test failure, which was mainly attributed to inadequate fetal fraction or technical limitations of the assay.

In the present study comprising 100 high-risk pregnant women, the diagnostic performance of non-invasive prenatal testing (NIPT) was evaluated against confirmatory invasive testing. For trisomy 21, NIPT correctly identified 6 patients (6%) as true positives and 92 patients (92%) as true negatives, with 1 false positive (1%) and 1 false negative (1%), showing highly significant diagnostic accuracy ($p < 0.0001$). For trisomy 18, 3 patients (3%) were true positive and 94 patients (94%) were true negative, while 2 patients (2%) showed false-positive results and 1 patient (1%) was false negative, demonstrating statistically significant concordance ($p < 0.001$). Similarly, for trisomy 13, NIPT detected 2 patients (2%) as true positives and 95 patients (95%) as true negatives, with 2 false positives (2%) and 1 false negative (1%), also showing strong statistical significance ($p < 0.001$).

In the present study, pregnancy outcomes were analyzed in relation to non-invasive prenatal testing (NIPT) results among 100 high-risk pregnant women. Among the 10 patients classified as NIPT high risk, 8 patients (80%) had confirmed fetal aneuploidy on invasive diagnostic testing, while 2 patients (20%) showed normal fetal karyotype. In contrast, among the 88 patients with NIPT low-risk results, 87 patients (98.86%) had normal pregnancy outcomes, whereas only 1 patient (1.14%) was later found to have confirmed aneuploidy. The association between NIPT risk category and final pregnancy outcome was found to be highly statistically significant ($p < 0.0001$) .

DISCUSSION

In the present study of 100 high-risk pregnant women, the majority of participants belonged to the advanced maternal age group (≥35 years), and advanced maternal age remained the most common indication for NIPT (40%). A similar pattern was observed in the study by Norton et al. [11] and Bianchi et al. [12], where advanced maternal age was the leading indication for cell-free fetal DNA testing, reflecting consistent global practice patterns in prenatal screening.

In the present study, abnormal biochemical screening (25%) and abnormal ultrasound findings (20%) were also significant indications for NIPT. Comparable findings were reported by Gil et al. [13] and Pergament et al. [14], who demonstrated that combined biochemical screening abnormalities and ultrasound soft markers significantly increase the indication for cfDNA testing.

In the present study, the majority of NIPT results were low risk (88%), while 10% were high risk and 2% were test failures. These findings are consistent with Bianchi et al. [12] and Norton et al. [11], who reported that most pregnancies undergoing NIPT are classified as screen negative, confirming the high negative predictive value of the test.

Regarding diagnostic accuracy, the present study demonstrated high concordance of NIPT with invasive testing for trisomy 21, 18, and 13, with minimal false-positive and false-negative rates. Similar high diagnostic performance has been reported by Chiu et al. [15], Norton et al. [11], and Gil et al. [13], who observed high sensitivity and specificity of cfDNA testing, particularly for trisomy 21 (>99%).

The present study also showed strong predictive accuracy of NIPT in relation to pregnancy outcomes, with 80% of high-risk cases confirmed as aneuploidy and 98.86% of low-risk cases showing normal outcomes. Similar findings were reported by Grati et al. [16] and Pergament et al. [14], who highlighted strong correlation between NIPT high-risk results and confirmed fetal chromosomal abnormalities, though false positives may still occur.

Overall, the present study findings reinforce the high clinical utility of NIPT as a reliable screening tool in high-risk pregnancies. This is supported by large meta-analyses by Taylor-Phillips et al. [17] and Gil et al. [18], which confirmed superior diagnostic performance of cfDNA compared to conventional screening methods. However, consistent with Bianchi et al. [12], confirmatory invasive testing and genetic counseling remain essential before final diagnosis.

CONCLUSION

The present study highlights that non-invasive prenatal testing (NIPT) is a highly effective and reliable screening modality for detecting fetal chromosomal abnormalities in high-risk pregnancies. Advanced maternal age remains the most common indication for testing, followed by abnormal biochemical screening and ultrasound findings, reflecting its increasing integration into routine prenatal care for risk-based assessment.The study demonstrates that most pregnancies are categorized as low risk on NIPT, with a small proportion showing high-risk results or test failures. Importantly, NIPT shows strong concordance with confirmatory invasive diagnostic methods, particularly for common trisomies, indicating high diagnostic accuracy and clinical reliability.Furthermore, the strong association between NIPT results and actual pregnancy outcomes emphasizes its usefulness in early risk stratification. However, the presence of occasional false-positive and false-negative results underscores the necessity of confirmatory diagnostic testing before making definitive clinical decisions.Overall, NIPT serves as a valuable, non-invasive, and highly sensitive screening tool that improves prenatal detection of chromosomal abnormalities while reducing the need for unnecessary invasive procedures, thereby enhancing overall prenatal care and counseling.

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